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Original Contribution

Milk Intake in Early Life and Risk of Advanced Prostate Cancer

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The authors investigated whether early-life residency in certain areas of Iceland marked by distinct differences in milk intake was associated with risk of prostate cancer in a population-based cohort of 8,894 men born between 1907 and 1935. Through linkage to cancer and mortality registers, the men were followed for prostate cancer diagnosis and mortality from study entry (in waves from 1967 to 1987) through 2009. In 2002–2006, a subgroup of 2,268 participants reported their milk intake in early, mid-, and current life. During a mean follow-up period of 24.3 years, 1,123 men were diagnosed with prostate cancer, including 371 with advanced disease (stage 3 or higher or prostate cancer death). Compared with early-life residency in the capital area, rural residency in the first 20 years of life was marginally associated with increased risk of advanced prostate cancer (hazard ratio = 1.29, 95% confidence interval (CI): 0.97, 1.73), particularly among men born before 1920 (hazard ratio = 1.64, 95% CI: 1.06, 2.56). Daily milk consumption in adolescence (vs. less than daily), but not in midlife or currently, was associated with a 3.2-fold risk of advanced prostate cancer (95% CI: 1.25, 8.28). These data suggest that frequent milk intake in adolescence increases risk of advanced prostate cancer.

adolescent; diet; Iceland; milk; prostatic neoplasms; risk factors

Abbreviations: AGES, Age, Gene/Environment Susceptibility; CI, confidence interval; HR, hazard ratio; IGF-1, insulin-like growth factor 1; OR, odds ratio.

Prostate cancer is one of the most common malignancies in the Western world (1), and its etiology remains largely unknown. Most (2–8) but not all (9) epidemiologic studies have found milk intake during adult life to be associated with an elevated risk. The association is largely limited to advanced disease (3, 10), and studies of screen-detected or early-stage disease tend to be null (9). This difference is important, given the substantial heterogeneity in the biologic potential of prostate cancer and the need to identify risk factors and opportunities for prevention of advanced disease.

Early-life diet may be important in the pathogenesis of prostate cancer, particularly around puberty when the prostate grows and matures. Few studies have addressed milk intake in early life and prostate cancer risk. A Swedish study found no association between early-life exposure to dairy products and risk of prostate cancer (11), and in the Boyd Orr cohort study, van der Pols et al. (12) found reduced risk with increased childhood consumption of milk. Studying early-life exposure is challenging because of a lack of variation in intake patterns and the need for follow-up over many decades.

In the early and mid-20th century in Iceland, there was considerable variability in dietary habits between residential areas because of the relative isolation of some regions. A 1939 household questionnaire found that consumption of milk was 4 times higher in rural areas than in seaside villages and twice that in the capital, Reykjavik (13). Thus, Iceland represents a natural experiment with which to study dietary patterns in early life.

Nationwide cancer registers began to be kept in Iceland in 1955 (14). The age-standardized incidence of prostate cancer

in Iceland has increased dramatically to become one of the highest in the world: 100.6 per 100,000 men in 2004–2008 (15; http://www.cancerregistry.is). Using these population-based data sources and the well-characterized Age, Gene/Environment Susceptibility (AGES)-Reykjavik cohort, we investigated whether residency-dependent milk consumption in early life was associated with the risk of prostate cancer.

MATERIALS AND METHODS

Study population

The Reykjavik Study is a population-based prospective cohort study that was initiated in 1967 by the Icelandic Heart Association. All men living in the capital area in December 1966 and born between 1907 and 1935 were identified ($n = 14{,}923$), and a random set of 12,842 men were invited to undergo examinations at different stages between 1967 and 1987; 9,115 men responded (71% response rate) (16–18). We excluded men diagnosed with prostate cancer prior to entry ($n = 19$) and those with incomplete follow-up ($n = 20$), which left 9,076 men in our cohort.

The examination included a detailed medical examination and completion of a health-related questionnaire, including questions on place of birth and residence history. For our analysis, we only used data from the first clinical visit or entry into the study. A subgroup of 2,268 participants were later enrolled in the AGES-Reykjavik Study, which was initiated in 2002, and completed a questionnaire about diet in youth, in midlife, and at present, as described by Harris et al. (19) (see Figure 1).

Classification of residency

Participants provided information on residency from birth throughout their lives. Participants listed all the places they had lived for 5 years or more. Although all participants were residing in the greater Reykjavik area in 1967 upon entry into the study, 64% had been born and raised in the countryside before moving to Reykjavik.

We classified every nonurban community as either a rural area or a seaside village by using the 1974 National Land Survey of Iceland and Icelandic historical statistics on population density by region in 1940 and fish catch by place of processing in 1942 (20). We classified 245 communities into 4 categories: Reykjavik, seaside villages, rural areas, and combinations of seaside villages and rural areas. Rural areas were areas away from the sea or areas by the sea which had no fishing industry and were classified as rural in the Icelandic historical statistics. Seaside villages were areas by the sea that had a fishing industry and were classified as densely populated. For the residency analysis, we excluded communities classified as a combination of a rural area and a seaside village.

Of the 9,076 subjects, information on first residency was available for 8,894 men who had not been diagnosed with prostate cancer before entering the Reykjavik Study (Figure 1). Of those, we excluded 303 whose first residency had been in a combination seaside village and rural area, leaving 8,591 men in the residency analysis.

Dietary habits in early life, midlife, and late life

In the AGES-Reykjavik Study, 2,268 men, including men with a prior diagnosis of prostate cancer, provided information on dietary habits in early life (ages 14–19 years), in midlife (ages 40–50 years), and at the present time using a validated food frequency questionnaire (21). The food frequency questionnaire obtained information on frequency of intake of milk and milk products (hereafter referred to as milk) and 9 other food groups for each time period, with the following response categories: 1) never, 2) less than once a week, 3) 1–2 times per week, 4) 3–4 times per week, 5) 5–6 times per week, 6) daily, and 7) more than once a day. The 9 other food groups were meat, fish, blood sausage or liver sausage, potatoes, fruits, vegetables, oatmeal, rye bread, and fish liver oil. The type of milk consumed was categorized as low-fat, whole, skim, or whey.

Covariate assessment

Information on possible confounders was retrieved from the questionnaire or examination completed at study entry. We recorded birth year, age at entry into the study, history of prostate disease in the family, whether the participant went regularly to a physician for a health check-up (at least every third year), and education. Education was categorized as elementary school, secondary school, college education (upper secondary schooling), or university education.

Body mass index (weight (kg)/height $(m)^2$) was calculated at enrollment, and participants were categorized by obesity status ($\geq$30 (obese) vs. $<$30 (nonobese)). Participants were considered to have type 2 diabetes if they had a self-reported history of diabetes or had a fasting blood glucose level of $\geq$126 mg/dL at enrollment (16). Information on nutritional factors in early life, in midlife, and at present, other than milk intake (such as intake of fish liver oil, fish, meat, rye bread, fruits, and vegetables), was obtained for the subgroup that completed the food frequency questionnaire in 2002–2006 (21).

Follow-up and ascertainment of outcome

We ascertained prostate cancer diagnoses through the Icelandic Cancer Registry (14, 22; http://www.cancerregistry.is). Information on cause of death was obtained from Statistics Iceland. Classification of tumor stage at diagnosis was based on medical records. Tumors were classified as stage I (incidental finding), including T1a, NX/0, and MX/0; stage II (tumor confined to prostate gland), including T1b/1c/1/2, NX/0, and MX/0; stage III (tumor extending through prostatic capsule), including T3, NX/0, and MX/0; or stage IV (locally advanced or metastatic disease), including T4, NX/0, and MX/0 or any T, N1, and/or M1. Stage information was available for approximately 61% of cases. Men who died from prostate cancer or had a stage III or IV tumor at diagnosis were classified as having advanced prostate cancer.

Participants were followed from study entry (between 1967 and 1987) to diagnosis of prostate cancer (first diagnosis in 1971), death, or the end of the observation period (December 31, 2009). Because the Icelandic government uses a computerized national roster that includes a unique personal

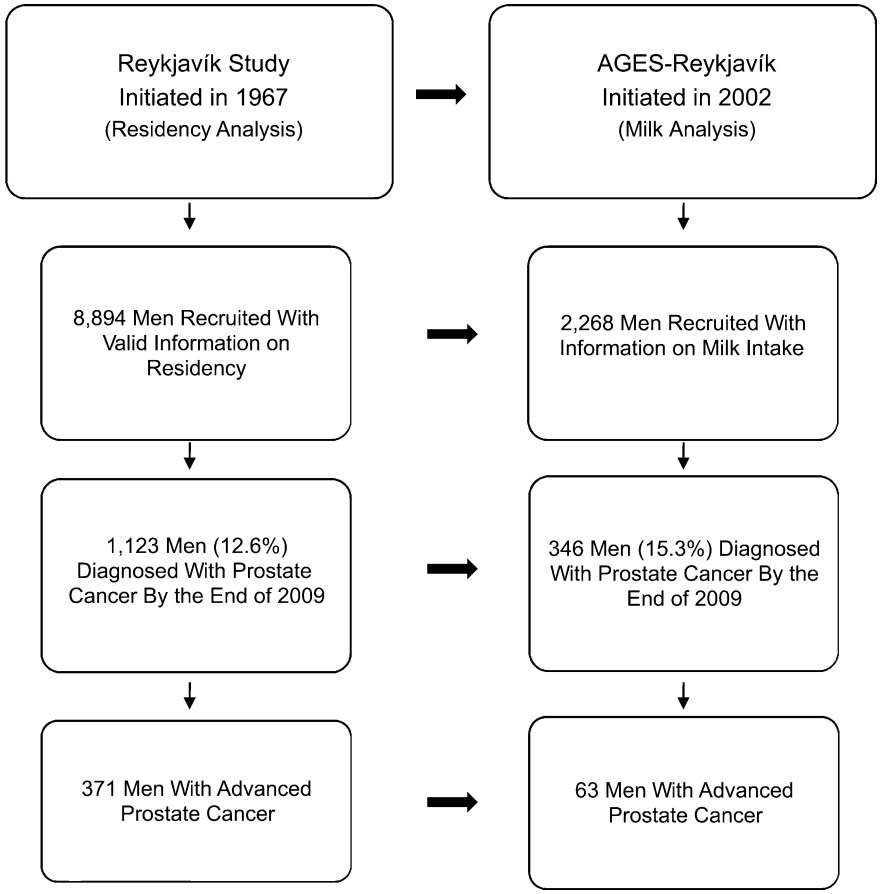

Figure 1. Selection of participants from the Reykjavik Study and the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, Iceland, 1967–2009.

identification number for each person, follow-up was virtually complete (23).

Statistical analyses

We used Cox proportional hazards regression models to calculate hazard ratios and 95% confidence intervals for localized or advanced prostate cancer according to residency (rural area or seaside village) in early life, with residence in the capital (Reykjavik) as the reference category. We adjusted our models for birth year (continuous), age at study entry (years; continuous), height (cm; continuous), body mass index ($\geq$30 vs. $<$30), type 2 diabetes, family history of prostate disease, seeing a physician regularly, and educational attainment (3 categories: elementary or secondary school, college education, or university education). We also explored the associations within strata of duration at first residency (moving from the first residence before or after 20 years of age). Our own data and previous work (24) indicated that the contrasts in diet were more extreme in earlier years; thus, we dichotomized birth year at 1920 in order to study whether the association between early-life residency and prostate cancer was stronger in earlier birth cohorts.

The milk analysis was based on a subgroup of men who completed the food frequency questionnaire, including men with combined residency. In this analysis, we used binary logistic regression models to calculate odds ratios and 95% confidence intervals for advanced and localized prostate cancer, since the cancer cases were both incident and prevalent. We contrasted the odds of prostate cancer among high (daily or more often) and low (less than daily) consumers of milk in early life, as well as according to midlife and current milk consumption. We created the cutpoint based on extreme intake of milk in early life, while retaining proportions sufficient for meaningful analysis. Low intake groups (less than daily) represented 20.4% of the participants, and the high intake group (daily or more) represented 79.6% (with 14.8% of men consuming milk more than once a day). We adjusted our models for birth year (continuous), age at study entry (continuous), height (continuous), body mass index ($\geq$30 vs. $<$30), type 2 diabetes, education (in 3 categories, as above), family history of prostate disease, and seeing a physician regularly. In a third model, we further adjusted for consumption of fish (in 3 categories: $\leq$2 portions per week, 2.1–4.0 portions per week, and $\geq$4.1 portions per week), fish oil (never vs. once a week or more), meat ($\leq$4 times per week vs. $\geq$5 times per

week), and rye bread (daily or more often vs. less than daily).

In a sensitivity analysis, we used binary logistic regression models to calculate odds ratios and 95% confidence intervals for total and advanced prostate cancer according to milk intake for incident cases only, adjusting for the same covariates as in the third model for milk intake.

For all statistical analyses, we used PASW software, version 18.0 (SPSS Inc., Chicago, Illinois; www.spss.com). The study protocol was approved by the Icelandic Ethical Review Board and the Icelandic Data Protection Authority.

RESULTS

In the Reykjavik Study, 37% of men had their first residence in Reykjavik, 34% in a seaside village, and 29% in a rural area. Table 1 shows the characteristics of the cohort ($n = 8,591$) by first residency. Average duration of first residency was longest among those with first residence in Reykjavik, because the majority never moved away. Participants with first residency in rural areas were equally distributed within the 2 birth cohorts, but participants who came from Reykjavik or a seaside village were more likely to be in the younger birth cohort (1921–1935). Men with first residency in rural areas were leaner and had less type 2 diabetes. Mean age at prostate cancer diagnosis was 73.1 years ($n = 360$) for men with early-life residency in Reykjavik, 73.9 years ($n = 383$) for men from seaside villages, and 74.6 years ($n = 335$) for men from rural areas.

Table 2 shows the characteristics of the subpopulation ($n = 2,267$) who gave information about milk intake in early life. Most ($n = 1,930$) were from the younger birth cohort (born after 1920). A majority (80%) had consumed milk and milk products daily in adolescence. Compared with those who did not consume milk and milk products daily, the high milk-intake group was more likely to be rural (29% vs. 19%), more likely to have a university education, more likely to have prostatic disease in the family, and less likely to smoke. Only 0.7% had never consumed milk or milk products in adolescence. Virtually all (98%) of the participants had consumed whole milk when they were teenagers; 83% of them consumed whole milk in midlife, and 31% in late life.

Early-life residency

During an average follow-up period of 24.3 years (standard deviation, 10.9), 1,078 men were diagnosed with prostate cancer, 351 with advanced disease. Mean age at diagnosis was 73.8 years.

We observed a marginal association between rural residency for the first 20 years of life and advanced prostate cancer, with a hazard ratio of 1.29 (95% confidence interval (CI): 0.97, 1.73) compared with early-life residency in Reykjavik. First residency in a seaside village, irrespective of duration, was not associated with advanced prostate cancer (hazard ratio (HR) = 1.07, 95% CI: 0.82, 1.39). We further explored the association between advanced prostate cancer and first residency in a rural area by birth period and duration of residency. Compared with men with first residency in Reykjavik, men with first residency in rural areas and born before 1920 had a hazard ratio of 1.70 for advanced prostate cancer (95% CI: 1.14, 2.53), irrespective of duration of first residency (Table 3). In contrast, no association was present among men from rural areas who had been born after 1920 (HR = 0.90, 95% CI: 0.62, 1.31). The *P* value for interaction between early-life rural residency and birth cohort was 0.125. There was no statistically significant association between early-life residency and diagnosis of localized prostate cancer (Table 3).

Milk intake

Of the 2,267 men who provided information on early-life milk intake, 346 had a prostate cancer diagnosis; 213 cases were diagnosed before completion of the food frequency questionnaire and 133 incident cases were diagnosed later during follow-up. Information on tumor stage at diagnosis was available for 258 men (75%), and 63 had advanced disease. Table 4 presents odds ratios and 95% confidence intervals for advanced and localized prostate cancer by milk intake in adolescence and mid- and late life.

Compared with less than daily intake, men with a high milk intake (at least once a day) in early life were more likely to have been diagnosed with prostate cancer (odds ratio (OR) = 1.58, 95% CI: 1.14, 2.18); intake of milk in midlife was unassociated with risk (OR = 1.11, 95% CI: 0.86, 1.44). High milk intake in adolescence was associated with over a 3-fold increased risk of advanced prostate cancer in the age-adjusted model and in the multivariate model adjusting for lifestyle and other dietary factors (OR = 3.22, 95% CI: 1.25, 8.28). When residency was added to the model, the risk estimate for early-life milk intake was only somewhat attenuated (OR = 2.89, 95% CI: 1.12, 7.48). No statistically significant associations were observed between frequent milk intake in midlife and advanced prostate cancer in any of the models. High milk intake in early life was marginally associated with localized prostate cancer risk (OR = 1.40, 95% CI: 0.99, 1.97) but not midlife consumption (OR = 1.03, 95% CI: 0.80, 1.34). We found no significant association between current high milk intake and risk of advanced prostate cancer (OR = 1.36, 95% CI: 0.80, 2.33).

Sensitivity analysis

To address potential recall bias or differential survival, we performed a sensitivity analysis limited to men with incident prostate cancer ($n = 133$) in the AGES-Reykjavik Study; only 27 were diagnosed with advanced disease. Compared with men consuming milk less than once per day, the odds ratio for total prostate cancer in the multivariate model was 1.38 (95% CI: 0.85, 2.25). The odds ratio for advanced disease among men with a high milk intake in adolescence was 2.14 (95% CI: 0.62, 7.39).

DISCUSSION

With limited infrastructure and isolated residential areas in Iceland during the early 20th century, the diets of many of these areas' inhabitants were largely limited to locally

Table 1. Characteristics of Male Participants in the Reykjavik Study According to the Location of Their First Residence, Iceland, 1967–2009

	Location of First Residence											
	Reykjavik Area (n = 3,188)				Seaside Village (n = 2,944)				Rural Area (n = 2,459)			
	No.	%	Mean (SD)	Median	No.	%	Mean (SD)	Median	No.	%	Mean (SD)	Median
Duration of residence at first location, years			44.0 (14.2)	47			21.9 (12.5)	20			19.8 (8.9)	20
Age at first visit[a], years			51.2 (8.3)	51			52.2 (8.5)	52			53.7 (8.7)	53
Height at first visit[a], cm			177.0 (6.4)				176.1 (6.2)				176.2 (6.3)	
Height by birth period, cm												
1907–1920	1,078	34	174.5 (6.1)		1,203	41	174.1 (6.0)		1,234	50	174.8 (6.0)	
1921–1935	2,110	66	178.3 (6.2)		1,741	59	177.5 (5.9)		1,225	50	177.5 (6.2)	
Body mass index[b] at first visit[a]			26.0 (3.6)				25.7 (3.4)				25.6 (3.3)	
Age group at first visit[a], years												
33–40	346	11			265	9			155	6		
41–50	1,124	35			1,005	34			750	31		
51–60	1,338	42			1,203	41			1,065	43		
61–70	306	10			360	12			356	15		
71–79	74	2			111	4			133	5		
Year of first visit[a]												
1967–1970	1,104	35			1,049	36			821	33		
1971–1980	1529	48			1,403	48			1,276	52		
1981–1987	555	17			492	17			362	15		
Education												
Primary and secondary	2,477	78			2,357	80			1,877	76		
College (postsecondary)	411	13			365	12			279	11		
University	300	9			222	8			303	12		
Prostate disease in the family	257	8			260	9			219	9		
Regular health check-up	744	23			612	21			480	20		
Diabetes type 2 at first visit[a]	155	4.9			133	4.5			74	3.0		
Body mass index $\geq$30	363	11.4			285	9.7			211	8.6		
Smoking status at first visit[a]												
Never smoker	581	18			599	20			627	25		
Former smoker	718	23			676	23			615	25		
Current smoker	1,889	59			1,669	57			1,217	50		
Entry into the AGES-Reykjavik Study in 2002–2006	816	26			725	25			597	24		
Consuming milk in adolescence more than once a day[c]	110	14			90	12			118	20		

Abbreviations: AGES, Age, Gene/Environment Susceptibility; SD, standard deviation.

[a] Participants underwent the first clinical examination (first visit) between 1967 and 1987.

[b] Weight (kg)/height $(m)^2$.

[c] Data were available only for those men who entered the AGES-Reykjavik Study.

Table 2. Characteristics of Male Participants in the AGES-Reykjavik Study Who Gave Information on Milk Intake in Adolescence, Iceland, 1967–2009

	Milk Intake in Adolescence							
	High[a] (n = 1,804)				Low[b] (n = 463)			
	No.	%	Mean (SD)	Median	No.	%	Mean (SD)	Median
Age at entry into AGES-Reykjavik, years			76.5 (5.4)	76			76.6 (5.3)	76
Height at first visit[c], cm			178.1 (6.1)				177.4 (5.9)	
Body mass index[d] at first visit[c]			25.4 (3.1)				25.6 (3.0)	
Education								
Primary and secondary	1,301	72			365	79		
College (postsecondary)	257	14			55	12		
University	246	14			43	9		
Prostate disease in the family	187	10			38	8		
Regular health check-up	327	18			93	20		
Diabetes type 2 at first visit[c]	31	1.7			7	1.5		
Smoking status at first visit[c]								
Never smoker	476	26			98	21		
Former smoker	430	24			100	22		
Current smoker	898	50			265	57		
Location of first residence[e]								
Reykjavik	648	36.7			168	37.5		
Seaside village	543	30.7			182	40.6		
Rural area	512	29.1			85	19.0		
Combination of rural area and seaside village	61	3.5			13	2.9		
Body mass index $\geq$30 at first visit[c,f]	127	7.1			36	7.8		

Abbreviations: AGES, Age, Gene/Environment Susceptibility; SD, standard deviation.
[a] Once a day or more.
[b] Less than once a day.
[c] In midlife when entering the Reykjavik Study.
[d] Weight (kg)/height $(m)^2$.
[e] Data on residency were missing for 15 men with low milk intake and 40 men with high milk intake.
[f] Information on body mass index was missing for 4 men in the high-milk-intake group.

produced food available on-site: fish from the sea or livestock raised on the farm. Thus, Iceland offers a unique setting in which to test hypotheses regarding early-life diet and cancer. We found that early-life residency in rural areas, particularly in the beginning of the 20th century, was associated with increased risk of advanced or lethal prostate cancer. Frequent milk intake at ages 14–19 years was associated with a 3-fold elevation in risk for advanced prostate cancer. These findings highlight the potential role of early-life diet in prostate cancer risk and are consistent with migrant studies showing that it takes at least 1 generation for migrants to incur the prostate cancer risk of the host country (25). Indeed, a study from Sweden found that immigrants entering Sweden in their 20s retained prostate cancer incidence rates similar to those of their native country (26).

An important strength of this prospective study was the large cohort and the extensive information on covariates. Further, record linkage to the Icelandic cancer registry permitted complete follow-up for prostate cancer diagnoses and deaths. By study entry, nearly all participants had equal access to the public health care system. Nevertheless, the study had several limitations. First, the classification of early-life residency into rural areas and seaside villages rested on geographic and historical evidence. Second, we had only crude information on the quantity of milk consumed in both adolescence and adulthood, because it was evaluated retrospectively by the participants, often several decades later. Our study may thus be vulnerable to recall bias, although a previous study indicated that recall of childhood food intake over 4 decades later can be as accurate as the reporting of current diet, especially for food items eaten rarely or daily (27). Also, to affect our results, recall bias would have had to be differentially associated with outcome. Men with prevalent prostate cancer may have evaluated their past milk consumption differently from men without prostate cancer. However, the fact that we found prostate cancer to be related only to early-life milk consumption, not midlife milk consumption, would argue against systematic overreporting of milk intake among prevalent prostate cancer patients. Furthermore, our sensitivity analysis limited to incident cases, although it had less statistical power, also suggested increased risk of prostate cancer with high milk intake in early life.

Table 3. Multivariate Analysis of Prostate Cancer Risk According to Early-Life Residency, Birth Period, and Duration of Residency, Iceland, 1967–2009

	No. of Participants	Mean Duration of Residency, years (SD)	Localized Prostate Cancer					Advanced Prostate Cancer				
			IR per 1,000 Person-Years	Age-Adjusted HR	95% CI	HR[a]	95% CI	IR per 1,000 Person-Years	Age-Adjusted HR	95% CI	HR[a]	95% CI
Birth period 1907–1920												
Location of first residence				($n = 277$)		($n = 275$)			($n = 176$)		($n = 176$)	
Reykjavik	1,080	50 (15)	3.67	1.00		1.00		1.67	1.00		1.00	
Seaside village	1,205	23 (13)	4.01	1.09	0.81, 1.47	1.09	0.81, 1.47	2.44	1.42	0.94, 2.15	1.43	0.94, 2.16
Rural area	1,235	21 (10)	3.90	0.98	0.73, 1.31	0.98	0.73, 1.32	3.13	1.67	1.13, 2.48	1.70	1.14, 2.53
Duration of residency in rural area[b]												
Age <21 years[c]	710	15 (5)	4.29	1.09	0.79, 1.52	1.10	0.79, 1.54	3.00	1.64	1.05, 2.54	1.64	1.06, 2.56
Age 21–60 years[c]	518	29 (8)	3.40	0.83	0.56, 1.23	0.82	0.56, 1.22	3.31	1.72	1.09, 2.73	1.77	1.12, 2.82
Birth period 1921–1935												
Location of first residence				($n = 450$)		($n = 448$)			($n = 175$)		($n = 174$)	
Reykjavik	2,116	41 (13)	2.99	1.00		1.00		1.32	1.00		1.00	
Seaside village	1,744	22 (12)	3.62	1.20	0.97, 1.48	1.21	0.98, 1.50	1.19	0.88	0.63, 1.25	0.88	0.63, 1.25
Rural area	1,231	19 (7)	3.27	1.05	0.83, 1.34	1.03	0.81, 1.31	1.32	0.92	0.63, 1.33	0.90	0.62, 1.31
Duration of residency in rural area[d]												
Age <21 years[c]	832	15 (5)	3.64	1.20	0.92, 1.56	1.18	0.91, 1.54	1.60	1.14	0.77, 1.70	1.11	0.74, 1.66
Age 21–60 years[c]	395	27 (6)	2.50	0.77	0.51, 1.15	0.73	0.48, 1.11	0.74	0.48	0.23, 1.00	0.49	0.24, 1.02

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; SD, standard deviation.

[a] Adjusted for birth year, age at entry, body mass index at entry, type 2 diabetes at entry, height at entry, family history of prostate cancer, regularly visiting a physician for a health check-up, and educational attainment.

[b] Data on duration of residency in a rural area were missing for 7 men because of misclassification.

[c] Age upon moving away from the rural area.

[d] Data on duration of residency in a rural area were missing for 4 men because of misclassification.

Table 4. Multivariate Analysis of Prostate Cancer Risk According to Milk Intake in Early Life, Midlife, and Late Life, Iceland, 1967–2009

Life Period, Tumor Stage, and Milk Intake	No. of Participants			Age-Adjusted OR	95% CI	Multivariate OR[a]	95% CI	Multivariate OR[b]	95% CI
	Total	Without Prostate Cancer	With Prostate Cancer						
Adolescent intake (ages 14–19 years)									
Advanced	2,267								
Low milk intake[c]		458	5	1.00	Referent	1.00	Referent	1.00	Referent
High milk intake[d]		1,746	58	3.11	1.24, 7.82	2.88	1.14, 7.26	3.22	1.25, 8.28
Localized	2,204								
Low milk intake		409	49	1.00	Referent	1.00	Referent	1.00	Referent
High milk intake		1,512	234	1.30	0.94, 1.80	1.26	0.90, 1.75	1.40	0.99, 1.97
Midlife intake (ages 40–50 years)									
Advanced	2,259								
Low milk intake		815	19	1.00	Referent	1.00	Referent	1.00	Referent
High milk intake		1,381	44	1.31	0.76, 2.27	1.28	0.74, 2.23	1.31	0.75, 2.29
Localized	2,196								
Low milk intake		713	102	1.00	Referent	1.00	Referent	1.00	Referent
High milk intake		1,202	179	1.03	0.79, 1.33	1.01	0.77, 1.31	1.03	0.80, 1.34
Current intake									
Advanced	2,265								
Low milk intake		1,045	23	1.00	Referent	1.00	Referent	1.00	Referent
High milk intake		1,157	40	1.44	0.85, 2.44	1.46	0.86, 2.49	1.36	0.80, 2.33
Localized	2,202								
Low milk intake		910	135	1.00	Referent	1.00	Referent	1.00	Referent
High milk intake		1,009	148	0.96	0.75, 1.24	0.95	0.74, 1.23	0.97	0.75, 1.26

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Adjustment was made for birth year, age, body mass index, type 2 diabetes, height, education, family history of prostate disease, and regular visits to a physician for a health check-up.

[b] Additional adjustments were made for consumption of fish, fish liver oil, meat, and rye bread.

[c] Less than once a day.

[d] Once a day or more.

Frequency of milk intake was not assessed in greater detail beyond "more than once per day," limiting our opportunities for assessing dose-response. Finally, because of incompleteness of information on tumor stage, some men with advanced disease at diagnosis were not classified as such. This probably produced underestimation of the association between milk intake and advanced prostate cancer.

We are aware of only 1 earlier study on both residency and dietary patterns in early life and risk of prostate cancer, a study from Sweden (11). In that study, rural residency in early life was associated with reduced risk of a prostate cancer diagnosis, which, as the investigators noted, could have been due to greater access to medical care and more prostate cancer diagnoses in more densely populated areas. Furthermore, it is unlikely that different residential areas in Sweden had variations in nutritional exposure as extreme as those observed in Iceland in the early 1920s. Our residency analysis showed an association with advanced prostate cancer only among participants born before 1920. Due to limited infrastructure in Iceland during the first decades of the 20th century, different residency areas were quite isolated and therefore characterized by distinct dietary differences, solidly documented by Sigurjonsson (13). Later, infrastructure was rapidly developed, particularly around World War II, increasing trade and opportunities for more diverse diets. This is reflected in our results indicating greater differences in milk intake between areas in the older birth cohort (1907–1920) compared with the younger birth cohort (1921–1935). Therefore, although other factors may have played a role, we hypothesize that greater dietary differences in the older birth cohort may explain the association between early-life residency in rural areas and risk of advanced prostate cancer later in life.

Most studies on prostate cancer have concentrated on midlife consumption. Only 2 studies have addressed early-life consumption of milk (11, 12). In the Swedish case-control study ($n = 256$ cases), Andersson et al. (11) found no association between early-life dietary factors, including milk intake, and total prostate cancer risk. Another study from the United Kingdom (the Boyd Orr Cohort Study), which collected

7-day weighed food record data from 1,352 families between 1937 and 1939, found that high dairy intake in childhood was associated with lower risk of prostate cancer (12). Neither of these studies provided an adequate distinction between advanced and localized prostate cancer, which may explain the discrepancy with our findings, along with differences in the exposure windows explored and different methods of collecting data on diet.

The men in our study predominantly consumed whole, unpasteurized cow's milk, particularly in rural areas in the early 20th century. Several mechanisms have been proposed for an influence of dairy food intake on prostate cancer risk. In a meta-analysis of case-control studies, circulating blood concentration of insulin-like growth factor 1 (IGF-1) was positively associated with the risk of prostate cancer, especially advanced disease (28). High milk consumption may increase plasma IGF-1 levels in middle-aged persons (29) and in adolescents and children (30, 31). IGF-1 levels in adulthood might be ''programmed'' by early-life nutrition (32); 2 studies have found early-life milk intake to reduce IGF-1 levels in adult life (33, 34), suggesting that the insulin-like growth factor pathway in adult life is not underlying our findings. On the other hand, it is possible that childhood milk consumption influences the risk of advanced prostate cancer later in life through elevated IGF-1 levels in the critical period of prostate development during puberty. Alternatively, high intake of calcium, a major nutrient in milk and milk products, may increase risk of prostate cancer by reducing levels of circulating 1,25-dihydroxyvitamin D (35), a hypothesized inhibitor of prostate carcinogenesis (36). Finally, diet-regulated hormonal influences, such as testosterone levels, start to exert an effect in utero and have an effect until early puberty (37). High intake of animal fat has been associated with increased testosterone levels (38), and high testosterone levels may influence prostate cancer risk (39). Thus, intake of dairy products may affect several pathways that are relevant for carcinogenesis in the prostate. Our findings suggest that teenage exposure may be of particular importance, but more studies are needed.

In summary, our data show that residency in rural areas and corresponding high milk intake in early life is associated with increased risk of advanced prostate cancer. While exploration of the relation of other rural dietary components in early life with prostate cancer risk is warranted, our findings also call for further studies on potential mechanisms underlying this association.

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